PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	22.11.2005
Applicant's or agent's file reference PN0369-PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NO2004/000286	28.09.2004	29.09.2003

Applicant
AMERSHAM HEALTH AS

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

DUE DATE:	—
FORMALITIES:	HCV
PAT. OFF:	MWW
ON DB:	21 NOV 05
CASE NO:	PN0369-PCT

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PN0369-PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/NO2004/000286	International filing date *(day/month/year)* 28.09.2004	Priority date *(day/month/year)* 29.09.2003
International Patent Classification (IPC) or national classification and IPC A61K49/00		
Applicant AMERSHAM HEALTH AS		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.07.2005	22.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Dullaart, A Telephone No. +31 70 340-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

10/573604
International application No.
PCT/NO2004/000286

IAP20 Rec'd PCT/PTO 28 MAR 2006

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-29 as originally filed

   Claims, Numbers

   1-12 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-12 in part

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-12 in part

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

Re Item III.

In the present application, the International Searching Authority has restricted the search because of the following objections under Articles 5 and 6 PCT.

Present claims 1-12 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds prepared in the examples, and those compounds specifically mentioned in the claims.

As it is not possible to form an opinion on unsearched subject-matter, the following must be limited accordingly.

Re Item V.

1 Reference is made to the following documents:

**D1: MALIK E et al: "Fluorescence diagnosis of endometriosis using 5-aminolevulinic acid"
Surgical Endoscopy, Vol. 14, no. 5, 2000, pages 452-455, XP002326510 ISSN: 0930-2794**

D2: WO 01/23005 A (SCHERING AKTIENGESELLSCHAFT; SCHIRNER, MICHAEL; LICHA, KAI; DINKELBORG) 5 April 2001 (2001-04-05)

D3: US 2003/162234 A1 (JALLAD KARIM N ET AL) 28 August 2003 (2003-08-28)

D4: WO 93/02192 A (REPLIGEN CORPORATION) 4 February 1993 (1993-02-04)

D5: WO 03/079015 A (VISEN MEDICAL, INC; POSS, KIRTLAND, G; MADDEN, KAREN, N; JONES, ELLA;) 25 September 2003 (2003-09-25)

**D6: SOUKOS, N. S. ET AL: "Monoclonal antibody-tagged receptor-targeted contrast agents for detection of cancers"
PROCEEDINGS OF SPIE-THE INTERNATIONAL SOCIETY FOR OPTICAL**

endometriosis.
Document D3 discloses a conjugate of folate and a fluorescent marker. Such a conjugate is also described in present example 1, and therefore falls within the scope of what is presently claimed.
Document D4 discloses in examples 9-10 the conjugate PF4 - fluorescein. PF4 targets angiogenesis, mentioned specifically in present claim 5 as a target for imaging endometriosis. According to the document, too, this conjugate allows for imaging of endometriosis: see the passage on page 1, lines 24-28.
Document D5 discloses claims the conjugate of a fluorochrome with a compound "selected from the group consisting of glucose, deoxyglucose, L-dopa, dopamine, thymidine, methionine, estradiol, acetate, raclopride, methyldiphosphonate, folate, a long-chain fatty acid, misonidazole, and a therapeutic compound". In the description, the same dye Cy5.5 as in the present application is linked to folate. The claims also specifically mention estradiol as targeting agent.
Document D10 discloses the conjugate of folate to a fluorescent dye.
These documents sufficiently describe the optical imaging agent as presently claimed. In some of these documents, the targeting agent is even the same as in the examples of the present application. Therefore, in view of these documents, the present application does not meet the requirements of Article 33.2 PCT for novelty.

More generally speaking, contrast agents which target angiogenesis, characteristic for *inter alia* endometriosis, but also for (pre)cancerous lesions, have been amply described in the prior art. As additional documents which illustrate this, the present authority further cites the following documents:
Document D6 discloses the conjugate of anti-EGFR-MoAb to Cy5.5. EGFR is expressed in many pre-cancerous lesions.
Document D7 discloses a fluorescent substrate for cathepsin B. This enzyme is expressed in fibrosarcoma HT1080. The fluorescent dye used is, like in the present application, Cy5.5.
Document D8 discloses the same dye as used un the present application, Cy5.5, attached through a polymer linkage to an antibody targeting angiogenesis. However, the experiments are performed in vitro.
Document D9 discloses the role of IL-8 in the pathogenesis of endometriosis. It also describes the intracellular conversion of calcein-AM to a fluorescent dye, used to detect

endometrial cells.
Document D11 discloses the detection of fluorescence of the peritoneal fluid in endometriosis patients after administration of 5-ALA.

Insofar as certain specific conjugates of a targeting agent and a fluorochrome may meet the requirements of Article 33.2 PCT for novelty, such conjugates should demonstrate an inventive step over the agents, which in the prior art are taught to target endometriosis. In the present application, however, the examples only describe the synthesis of 4 specific agents. On the other hand, in the prior art documents, several agents are used to detect endometrial tissue, either in vitro or in vivo. Therefore, as the level of disclosure of the present application seems to be less than in the prior art, the requirements of Article 33.3 PCT for inventive step have not been met.

3 CLAIMS 2-12
Dependent claims 2-12 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

Re Item VIII.

Claims 1-12, as well as the claims which depend from these, do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved (with/having affinity for an abnormally expressed biological target associated with endometriosis; detectable in in vivo optical imaging), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.